59. (New) A method for screening for an agent of claim 57, wherein the ligand is an anti-N-terminal FADD antibody.

60. (New) A method for screening for an agent of claim 57, wherein the FADD fragment or the agent is detectably-labeled.

II. REMARKS

Claims 1-5, 21, 23, 29, 30, 37-43, 45, 46, 48, 49, and 53-60 are pending in the subject application. Claims 1-5, 21, 23, 29, 30, 37-43, 45, 46, 48, 49, and 54-56 have been examined. Claim 53 has been withdrawn from consideration by the Office pursuant to an election/restriction requirement. Applicants expressly reserve their right to file one or more applications directed to the same or similar subject matter under 35 U.S.C. §120. By this Amendment, claims 1-5, 29-30, 37-43, 45 and 54-55 are amended to more clearly point out and distinctly claim the subject matter which Applicants regard as the invention. Support for the claim amendments can be found throughout the specification as filed. New claims 57-60 have been added. Support for claim 57 can be found in the language of the originally filed claims 29 and 30 as well as in the description at page 37, lines 25 through page 40, line 2 on performing cellular functional assays. Support for new claims 58-60 can be found at page 35, lines 4-23. An issue of new matter is not raised by these amendments, and entry thereof is respectfully requested.

In view of the preceding amendments and the remarks which follow, Applicants respectfully request that the Examiner reconsider and withdraw the rejections of the claims.

Informalities

The specification is objected to because of a typographical error at page 4, line 1, where "Figure 2B" should be "Figure 2C". By this amendment and response, the error has been corrected.

Claim 2 is objected to because it depends from allegedly distinct claim 53. Applicants maintain the position that that the subject matter of claim 53 is linked to the invention originally claimed. However, in an effort to expedite prosecution of the application, claim 2 is amended to eliminate its dependency on claim 53.

Objection to the drawings indicated by the Examiner is acknowledged. Correction will be made where needed before issuance of this application.

35 U.S.C. § 112, First Paragraph

As an initial matter, Applicants thank the Examiner for withdrawal of the rejections of various claims based on an alleged lack of enablement. The remaining rejections are addressed in the section that follows:

Claims 2, 29 and 30 remained rejected on the ground that the specification allegedly does not enabled to *"the full scope of a FADD protein identified by name."* The Office remarked that *"it is not clear that a single species of FADD protein (SEQ ID NO:2) would enable the skilled artisan to make other structurally different proteins that have the same biological activity"* (see page 5 of the previous Office Action dated September 5, 1997). With respect to claims 29 and 30, the Office opined that the specification, while being enabling for a method of screening for an agent that modulates the binding of FADD of SEQ ID NO:2 to the cytoplasmic domain of the Fas receptor, does not reasonably provide enablement for a method of screening for an agent useful to modulate a cellular function regulated by the Fas receptor pathway. Applicants respectfully traverse.

First, FADD protein of the instant invention is not simply identified by name but rather defined by structural characteristics, such as a specific sequence as shown in SEQ ID NO:2, and/or biological functions intrinsic to the FADD protein. The intrinsic functional properties as defined in the specification include the ability of FADD to interact with the cytoplasmic domain of the Fas receptor and the ability to induce apoptosis of a suitable cell (see pages 15-16 of the specification). Contrary to the Examiner's assertion that Applicants disclosed only a single species of FADD protein, Applicants, in fact, exemplified 6 distinct FADD analogs or fragments

thereof (one analog carrying a point mutation and some FADD fragments being truncated at the N-terminus or the C-terminus), that define the structural boundaries of a FADD fragment or an analog thereof that possesses either of the two aforementioned functional characteristics (see Figures 8A and 8B as well as Examples IV-XI of the specification). As expressly stated in the specification, the deletion analysis "suggests that, whereas the Fas interacting domain is in the C-terminal half of FADD, the death effector domain lies in the N-terminal portion" (see Example XI at page 53). The disclosure further specifies the N-terminal half of the full-length FADD protein having amino acid residues 1 through about 125 as shown in Figure 2A (see page 15, lines 25-27). Given the complete sequence of the FADD protein, anyone skilled in the art would recognize the C-terminal half fragment of the FADD protein that binds to the cytoplasmic domain of the Fas receptor. Accordingly, someone who is designing a fragment or an analog of the FADD protein and wishes to determine whether it falls within the scope of the claims can readily do so by comparing the sequence of the fragment with the sequences listed in the disclosure with reference to the limitations required by the claims. Therefore, one skilled in the art can readily practice the claimed invention without undue experimentation. Withdrawal of this rejection is respectfully requested. Applicants also note that in a sincere effort to place the claims in condition for allowance, the recitation of "the detectably-labeled FADD" is incorporated into claims 29 and 30 in accordance with the Examiner's suggestion.

Claim 45 remained rejected under 35 U.S.C. § 112, first paragraph for allegedly containing new subject matter. Specifically, the Office objected to the correction of the phrase "at amino acids 1 to 120 and 122 (instead of 123) to 208". It was contested that support for inclusion of one additional amino acid is not found at the indicated locations in the specification. Applicants respectfully traverse. Applicants previously pointed out that Figure 2B and page 4, line 4 describe non-conservative substitution of the valine residue at position 121 within the death domain of FADD, which disrupts binding and/or signaling of the respective protein. The rest of the amino acid residues, shown in part in Figure 2B and depicted entirely in Figure 2A and SEQ ID NO. 2, can contain conservative substitutions. The amendment was merely a correction of a typographical error.

Claims 1-5, 21, 23, 29, 30, 37-43, 45, 46, 48, 49 and 54-56 are rejected on the ground that the use of phrase "capable of" or "has the ability to" does not meet the enablement requirement. Without conceding the correctness of the Office's position, and merely to expedite examination, claims containing the objected terms have been amended to recite "binds to" and "induces" in accordance with the Examiner's suggestion.

35 U.S.C. § 112, Second Paragraph

Applicants acknowledge withdrawal of the rejections of various claims under 35 U.S.C. § 112, second paragraph. The remaining and newly introduced rejections are addressed as follows:

Claims 1, 3-5, 21, 37-39, 41-43, 46, 48-49, and 53-56 are rejected as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. The Office objected to the recitation of "FADD polypeptide", and asserted that the instant specification does not identify the material element or combination of elements which is unique to and definitive of "FADD polypeptide". It was suggested that the phrase "polypeptide" be used instead. Applicants traverse. The definition of "FADD protein" or "FADD polypeptide" is clearly specified under the section proteins and polypeptides at pages 13-14 of the disclosure. Briefly, the disclosure specifies a "FADD protein" or "FADD polypeptide" by amino acid sequence, molecular weight and/or biological functions. Given the structural and functional characteristics of FADD, one skilled in the art can readily understand the metes and bounds of these claims. Withdrawal of this rejection is respectfully requested.

Claims 1, 3-5, 37-43, 54 and 55 are alleged to be indefinite. The Office objects to the use of "capable of" and "has the ability to", as these terms allegedly do not recite a positive limitation but only requires the ability to so perform. The claims as amended recite "binds" or "induces" so as to remove the objected language in accordance with the Examiner's suggestion. Thus, these rejections have been overcome.

Claims 3 and 37-43 are alleged to be indefinite in not reciting an appropriate sequence identifier. Applicants traverse. These claims are variously dependent on claim 1, in which "SEQ ID NO:2" is recited to specify the sequence of the amino acid residues.

Finally, claims 29 and 30 are rejected on the ground that step "c)" is unclear in reciting the nature of the analysis to be taken place during a screen for agents that modulate Fas receptor pathway. Without conceding the correctness of the Examiner's position and merely to expedite examination, the claims as amended no longer contain the offending step. Furthermore, the claims are amended to emphasize the subject matter of the invention by reciting "a method for screening for an agent that inhibits binding of a FADD protein or polypeptide to the Fas receptor", which is based on the Examiner's suggestion.

Applicants believe that all the rejections on the grounds of indefiniteness have been adequately addressed and that the above amendments to the claims overcome the rejections. Therefore, it is respectfully requested that these rejections under §112, second paragraph, be withdrawn.

Rejections Under 35 U.S.C. § 102

The Office removed the previous rejections under 35 U.S.C. § 102(a) and 102(b) but introduced new rejection of claims 5, 46, 48, 55, and 56 under 102(a) in view of Boldin et al. This reference is cited for disclosing a polypeptide fragment that consists of at least the N-terminal portion of the FADD protein that is suspected to possess an inherent property of inducing cell apoptosis. The Examiner correctly noted that Boldin et al. do not disclose that the N-terminal fragment is capable of inducing cell apoptosis. In response to the rejection, a Declaration by Applicants Vishva M. Dixit and Karen O'Rourke, that is pursuant to 37 C.F.R. § 1.131, is submitted herewith. The facts recited in this Declaration establish that, prior to the publication date of the Boldin reference, the subject matter of claims 5, 46, 48, 55, and 56 were conceived and reduced to practice in this country. Specifically, the attached Cell paper authored by Applicants clearly documents the isolation of the full-length FADD polypeptide and the delineation of specific domains within the polypeptide that perform distinct functions including association with the Fas receptor and initiation of the programmed cell death. See Table 1 and Figure 7 at page 509 that demonstrate the N-terminal portion of FADD, or a fusion protein thereof being capable of inducing apoptosis in MCF7 and BJAB cells. Applicants' Cell paper was received by Cell Press for a review on February 23, 1995 and was last revised on March 31,

1995 (see page 511, last paragraph before the reference section), which was prior to the April 7, 1995 publication date of the cited reference.

Applicants' Declaration further establishes that the subject matter of these claims does not correspond to a lost count in an interference and is not otherwise barred. Thus, the application of the Boldin reference should be withdrawn.

Rejections Under 35 U.S.C. § 103

Applicants acknowledge withdrawal of the previous rejections under 35 U.S.C. § 103. No additional ground of rejection under this section was raised.

III. CONCLUSION

Applicants submit that the above discussion is fully responsive to all grounds of rejection set forth in the Office Action. In view of the comments above, Applicants respectfully request that all outstanding rejections be withdrawn, and that the pending claims, as amended, be allowed. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If a telephone interview would be of assistance in advancing prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicants' petition for any required relief including extensions of time and authorizes the Assistant

Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952 (Ref. 20344-2107020)**. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: December 11, 1998

Respectfully submitted,

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